CUTANEOUS LOCAL TOLERANCE OF DIPHOTERINE®

in human volunteers after an occlusive application during 48 hours

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Diphoterine® is an eye/skin decontamination solution for chemical splashes which contains an amphoteric compound. Its chemical and physical properties allow a quasi polyvalent rinsing of chemical splashes with a quick return to a physiological state. The local tolerance of Diphoterine® was evaluated on human volunteers after a single and occlusive application during 48 hours.

MATERIAL AND METHODS

The skin local tolerance was evaluated in 55 volunteers by IDEA (Dermatological Institute of Aquitaine), (study n°¨ID-07/0477 // 1.01-48H) Martillac, France). The investigation was carried out at Solar Test International (STI) in Romania, according to the internal standard protocol and ethical committee. A single application of 0.02ml of Diphotérine® (batch N°. D970112B) was applied on the outside surface of the arm and maintained for 48 hours in contact with the skin, with the help of an occlusive patch (Haye's Chambers). 57 volunteers were recruited, male and female, with normal skin, without any dermatological lesion on the experimental area, were included in the study. There were 8 volunteers aged 65 to 70 years old but this had no influence on the results. The clinical evaluation was made 30 minutes after the patch removal and takes in account the erythema, the papules, the vesicles and blisters. According to their intensity, the value of the irritation ranges from 0 to 4. The total sum of the scores, divided by the number of volunteers, defines the average irritation index which allows the product to be classified *(Table 2)*.

non irritant	I.I.M. ≤ 0.20
slightly irritant	0.20 < I.I.M. ≤ 0.5
moderately irritant	0.50 < I.I.M. ≤ 2
very irritant	2 < I.I.M. ≤ 3
severely irritant	I.M.M. > 3

Table 2: *Irritation index*

RESULTS

Of the 57 recruited volunteers, 55 were included in the study. The average index of irritation I.I.M. for Diphotérine® is 0.00.

DISCUSSION

The results of this test show that Diphoterine® did not induce skin irritation. It is in accordance with the results obtained in a previous test where local tolerance was evaluated in the rabbit on both normal and scarified skin, by non-occlusive or semi-occlusive application. Semi-occluded application was used to mimic contact of wet clothes soaked with Diphotérine® and non-occluded application for Diphotérine® itself on skin as recommended protocol. No irritating or toxic effect was observed.

Skin sensitization study in the guinea pig has been also performed following the Magnusson and Kligman method and published. Other toxicological tests have also been performed in order to evaluate the toxicity of Diphotérine® by other routes of exposure. The acute toxicity of the product Diphoterine® was also evaluated in the rat by the oral route. The LD50 of the product Diphoterine® administered by the oral route in rats was found greater than 2000 mg/Kg, a dose at which no signs of toxicity were observed : no deaths, no change of general behavior or bodyweight and no evidence of macroscopic abnormalities when necropsy was performed. The Ames test has also been performed and Diphotérine® did not show any mutagenic activity in the bacterial reverse mutation test with Salmonella typhimurium and Escherichia coli.

The conditions of exposure, used for the evaluation of local tolerance in human volunteers, are much more severe than what is required by the standard protocol of the use of Diphotérine® for decontamination of chemical splashes: a unique dose within one minute of contact, 500 ml for washing one eye and 5 liters during 5 minutes for the complete body.

All these toxicological data are in accordance with the post-marketing surveillance program of Diphoterine® use where no adverse effects of this eye/skin chemical splash decontamination solution have been noted.

These innocuousness data open the range for the use of different dermal applications of Diphoterine®, such as delayed management of chemical splashes in victims of chemical assaults for which more and more countries are now concerned by this problem.

A comparative clinical study between saline solution versus Diphoterine® on eye burns has already shown the interest of its delayed use: for grade 1 and grade 2 burns, reepithelialisation time is shorter when rinsing has been done with Diphotérine®: 1.9 ± 1 day, compared with 11.1 ± 1.4 days (p = 10-7) and 5.6 ± 4.9 days compared with 10 ± 9.2 days (p = 0.02).

An experimental and comparative study of a concentrated hydrochloric acid burn on rat skin showed that skin flushing with Diphoterine® stopped the burn evolution and reduced substance P release and higher concentrations of b-endorphin were observed compared to other washing solutions.

CONCLUSION **Diphotérine® can be considered as non-irritant after a single application of 48 consecutive hours.**

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